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ORIGINAL ARTICLE

Low thyroid function is associated with metabolic dysfunction-associated steatotic liver disease

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Key words
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Abstract

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is recently introduced to better highlight the pathogenic significance of cardiometabolic dysfunction, as compared with non-alcoholic fatty liver disease. This study aimed to investigate the association between low thyroid function and MASLD in the new context.
Methods: We recruited 2901 participants for our retrospective cohort study from 2016 to 2021. Participants were divided into strict-normal thyroid function and low thyroid function groups (low-normal thyroid function, subclinical hypothyroidism) based on initial thyroid stimulating hormone (TSH) levels, respectively. Cox regression models were used to estimate the hazard ratios (HRs) and 95% CI.
Results: During a median follow-up of 15.6 months, 165 (8.9%) strict-normal thyroid function subjects and 141 (13.4%) low thyroid function subjects developed MASLD; this result was statistically relevant ($P < 0.05$). Univariate regression analysis showed that low thyroid function and subclinical hypothyroidism were statistically significantly associated with MASLD (low thyroid function: HR1.53; 95% CI 1.22–1.92; subclinical hypothyroidism: HR1.95; 95% CI 1.47–2.60).
Conclusions: MASLD is associated with low thyroid function and the relationship between MASLD and low thyroid function is independent.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is of growing public health concern. A recent meta-analysis estimated that MASLD affects 32.4% of the global population.[1] Unfortunately, despite the severe morbidity and mortality burden of MASLD, there is currently no approved pharmacotherapy, and liver transplantation is often the only treatment for patients with decompensated MASH cirrhosis.[2,3] The occurrence and development of MASLD are closely related to metabolic syndromes, such as obesity, hypertension,

dyslipidemia, and insulin resistance. The thyroid hormone is an important hormone to maintain the normal metabolism of the body and has an important role in maintaining fat metabolism in the liver. Thyroid hormones play a vital role in the thyroid–liver axis and lipid metabolism.[4] Hypothyroidism can lead to metabolic disorders and thus affect the clinical progress of liver disease.[5] MASLD was a new term introduced in 2023 to replace non-alcoholic fatty liver disease (NAFLD).[6] Although the changes in the definition are subtle, they still have an impact on the prevalence and risk factors between MASLD and NAFLD.[7,8] Previous studies on the relationship between low thyroid function and fatty liver have mostly used fatty liver disease as defined by NAFLD. Recent studies investigating the relationship between low thyroid function and MASLD under new concepts and new diagnostic criteria have been insufficient and have yielded inconsistent results. Furthermore, existing research on the relationship between MASLD and thyroid function is predominantly based on Western populations.[9] Given the racial differences between Eastern and Western populations, our retrospective cohort study aims to investigate the relationship between low thyroid function and MASLD specifically among Eastern populations.

Methods

Data source and study design. This was a retrospective cohort study conducted between January 2016 and December 2021 in a hospital in Shanghai, China. We used the check-up database of adults from a hospital. Patients for whom health check-up data were available from 2016 to 2018 and ≥365 days after the date of the initial observation were enrolled ($n = 3605$). Among these subjects, 465 were excluded due to initial fatty liver disease; 212 were excluded due to lack of thyroid function test results; 27were excluded due to abnormal reference range of FT4 levels (FT4 <9.01 pmol/L and FT4 >19.04 pmol/L) and with thyroid stimulating hormone (TSH) levels under 0.45 mIU/L. Finally, 2901 adults were enrolled in our study. To compare whether a TSH within the upper normal range and subclinical hypothyroidism were independently associated with the incidence of MASLD, participants were divided into three groups based on initial TSH levels. The flowchart of participant selection is shown in Figure 1.

Disease definition. The diagnostic criteria for MASLD are based on ultrasound imaging evidence of hepatic fat accumulation (hepatocellular steatosis) combined with at least one of the following cardiometabolic risk factor: (i) BMI ≥23 kg/m^2 (by the Asia-Pacific Criteria); (ii) type 2 diabetes or fasting glucose levels ≥5.6 mmol/L; (iii) blood pressure ≥130/85 mmHg or specific drug treatment; (iv) plasma triglycerides ≥1.70 mmol/L; (v) plasma HDL-cholesterol ≤1.0 mmol/L for men and ≤1.3 mmol/L for women.[6]

Strict-normal thyroid function was defined as 0.45–2.5 mIU/L for TSH and normal FT4 level (reference ranges: FT4 9.01–19.04 pmol/L).[10] Low thyroid function was defined as a serum TSH level greater than or equal to 2.5 mIU/L, with a normal thyroid hormone (FT4) level. Among the patients with low thyroid function, low-normal thyroid function was defined as 2.5–4.5 mIU/L for plasma TSH, with a normal FT4 level.[11,12] Subclinical hypothyroidism was defined as a TSH level greater than or equal to 4.5 mIU/L, with a normal FT4 level. We utilized the fully automated chemiluminescent immunoassay analyzer, Abbott ARCHITECT i2000, manufactured by Abbott Laboratories in the United States, to measure thyroid function (FT4 and TSH levels).

Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg. Type 2 diabetes mellitus was defined as a fasting plasma glucose level of ≥6.5 mmol/L.

Statistical analysis. Categorical variables were summarized as percentages and continuous variables were summarized as means ± standard deviations. The covariates between different groups were compared using the Student's *t*-test or analysis of variance for continuous variables and the chi-square test for categorical variables. The cumulative incidence of MASLD events was estimated by the Kaplan–Meier method, and the log-rank test was applied to compare across groups. To control for potential confounding variables, univariable and multivariable Cox proportional hazard regression analyses were used to analyze the relationship between thyroid function and the development of MASLD. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of MASLD in different thyroid function groups were calculated. All the reported *P* values were two-tailed, and statistical significance was set at 0.05. All statistical analyses were performed using R statistical software version 4.2.1.

Results

Baseline characteristics. The retrospective cohort study included 2901 participants without prior MASLD. The median follow-up time was 15.6 months with an interquartile range of 14.3–23.0 months. The subjects were divided into two groups for follow-up, such as those who developed MASLD ($n = 306$) and those who did not ($n = 2595$). The clinical characteristics of the MASLD and non-MASLD groups are shown in Table 1. There were differences in the comparison between patients with MASLD and without MASLD except for platelets. Compared with the non-MASLD group, the MASLD group was more likely to be older, with a higher prevalence of T2DM and hypertension. Furthermore, the serum TSH level, serum LDL level, BMI, and glucose level were significantly higher, and the serum HDL level was significantly lower in the MASLD group than in the non-MASLD group.

Participants were divided into three groups based on initial TSH levels (1852 in the strict-normal thyroid function group, 650 in the low-normal thyroid function group, and 399 in the subclinical hypothyroidism group). During a median follow-up of 15.6 months, 165 (8.9%) strict-normal thyroid function subjects and 141 (13.4%) low thyroid function subjects developed MASLD; this result was statistically relevant ($P < 0.05$). Among low thyroid function subjects, 75 (11.5%) low-normal thyroid function subjects and 66 (16.5%) subclinical hypothyroidism subjects developed MASLD; this result was statistically relevant ($P < 0.05$). Age, sex, BMI, total cholesterol, triglycerides, AST, platelets, and albumin were all significantly different between the strict-normal thyroid function group and the low thyroid function group. The baseline characteristics of this cohort are shown in Table 2.

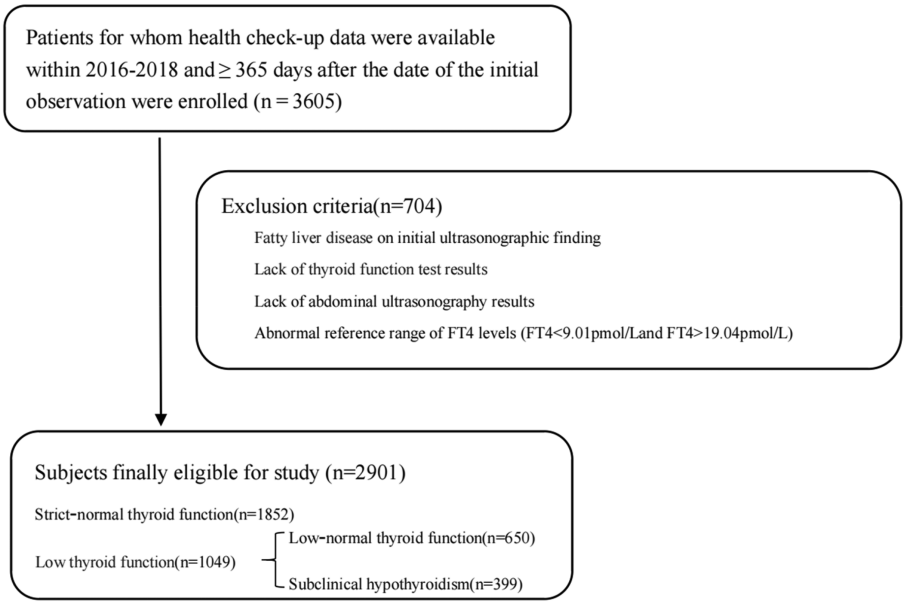

Figure 1 Flowchart of participant selection.

Table 1 Baseline clinical characteristics of the subjects grouped according to the development of MASLD during 2019–2021 ($n = 2901$)

Variables	MASLD ($n = 306$)	Non-MASLD ($n = 2595$)	*P*
Median (interquartile range) follow-up (m)	16.0 (23.0–14.3)	15.6 (23.0–14.3)	0.404
Age, year	51.70 ± 17.03	49.32 ± 18.00	0.028
Sex (male [*n*%])	179 (58.5)	1105 (42.6)	<0.001
BMI (kg/m^2)	25.00 ± 2.65	22.09 ± 2.64	<0.001
Total cholesterol, mmol/L	4.89 ± 0.92	4.70 ± 0.90	<0.001
HDL cholesterol, mmol/L	1.21 ± 0.28	1.42 ± 0.34	<0.001
LDL cholesterol, mmol/L	3.09 ± 0.79	2.90 ± 0.79	<0.001
Triglycerides, mmol/L	1.93 ± 1.51	1.23 ± 0.73	<0.001
ALT, U/L	23.45 ± 11.91	16.24 ± 8.70	<0.001
AST, U/L	20.57 ± 6.11	18.80 ± 5.52	<0.001
GGT, U/L	30.49 ± 18.15	21.25 ± 15.83	<0.001
TSH, mIU/L	3.06 ± 2.67	2.47 ± 2.27	<0.001
Glucose, mmol/L	5.36 ± 1.04	5.13 ± 1.03	<0.001
Platelets 10^9/L	222.12 ± 57.84	215.80 ± 59.06	0.076
Albumin, g/L	46.68 ± 2.81	46.22 ± 2.90	0.015
T2DM, *n*%	24 (7.8)	101 (3.9)	0.003
Hypertension, *n*%	228 (74.5)	1156 (44.5)	<0.001

Values are mean ± SD or frequency (%).
BMI, body mass index; HDL, high-density cholesterol; LDL, low-density cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transpeptidase; T2DM, Type 2 diabetes mellitus.

Incidence of MASLD according to the TSH levels. The cumulative incidence of MASLD in subjects with strict-normal thyroid function and low-normal thyroid function was 58.1 per 1000 person-years and 87.2 per 1000 person-years. Among low-normal thyroid function subjects, the cumulative incidence of MASLD in subjects with subclinical hypothyroidism and low-normal thyroid function was 74.5 per 1000 person-years and 108.0 per 1000 person-years. The results of the Kaplan–Meier analysis and the log-rank test for the cumulative incidence of MASLD are shown in Figure 2. The figure shows that the cumulative incidence of MASLD in the subclinical hypothyroidism group was significantly higher than in the strict-normal thyroid function group.

The association between thyroid dysfunction and MASLD. Univariate regression analysis showed that low thyroid function and subclinical hypothyroidism were statistically significantly associated with MASLD (low thyroid function: HR1.53; 95% CI 1.22–1.92; subclinical hypothyroidism: HR1.95; 95% CI 1.47–2.60). After multivariate adjustment for known risk factors, multivariate regression analysis showed that low thyroid function was an independent risk factor of MASLD (HR1.47, 95% CI 1.16–1.85). When low thyroid function was redefined based on the TSH level, subclinical hypothyroidism was found to be statistically significantly associated with MASLD (HR 1.73, 95% CI 1.29–2.33, Table 3).

Discussion

The principal finding of this retrospective cohort study was that MASLD was associated with low thyroid function, and the relationship between MASLD and low thyroid function was independent of age, sex, hypertension, T2DM, total cholesterol, and triglycerides. Additionally, this study also compared whether a TSH within the upper normal range and subclinical hypothyroidism were independently associated with the incidence of MASLD. Our result indicated that subclinical hypothyroidism

Table 2 Characteristics of participants based on TSH Levels ($n = 2901$)

Variables	Strict-normal thyroid ($n = 1852$)	Low thyroid function ($n = 1049$)	*P*	Low thyroid function ($n = 1049$)		*P**
				Low-normal ($n = 650$)	Subclinical ($n = 399$)	
Age, year	48.28 ± 17.35	51.85 ± 18.68	<0.001	50.53 ± 18.34	53.99 ± 19.05	0.004
Sex (male [*n*%])	893 (48.2)	391 (37.3)	<0.001	233 (35.8)	158 (39.6)	0.222
BMI (kg/m^2)	22.29 ± 2.71	22.57 ± 2.93	0.010	22.32 ± 2.85	22.98 ± 3.01	<0.001
Total cholesterol	4.69 ± 0.88	4.78 ± 0.95	0.009	4.72 ± 0.88	4.88 ± 1.04	0.011
HDL cholesterol	1.40 ± 0.34	1.40 ± 0.34	0.962	1.42 ± 0.34	1.37 ± 0.33	0.056
LDL cholesterol	2.90 ± 0.79	2.94 ± 0.80	0.284	2.90 ± 0.76	2.99 ± 0.86	0.061
Triglycerides	1.25 ± 0.74	1.39 ± 1.06	<0.001	1.31 ± 0.84	1.53 ± 1.34	0.002
ALT, U/L	16.91 ± 9.25	17.17 ± 9.53	0.474	16.25 ± 8.94	18.67 ± 10.25	<0.001
AST, U/L	18.63 ± 5.38	19.60 ± 5.96	<0.001	18.89 ± 5.66	20.77 ± 6.25	<0.001
GGT, U/L	22.35 ± 16.69	21.99 ± 15.70	0.563	20.53 ± 14.36	24.38 ± 17.44	<0.001
Glucose, mmol/L	5.14 ± 0.97	5.19 ± 1.13	0.188	5.19 ± 1.09	5.19 ± 1.19	0.999
Platelets 10^9/L	218.15 ± 57.97	213.49 ± 60.57	0.041	216.42 ± 61.46	208.70 ± 58.85	0.045
Albumin, g/L	46.38 ± 2.86	46.01 ± 2.94	0.002	46.06 ± 2.89	45.79 ± 3.20	0.006
T2DM, *n*%	79 (4.3)	46 (4.4)	0.879	24 (3.7)	22 (17.2)	0.162
Hypertension, *n*%	866 (46.8)	518 (49.4)	0.175	315 (48.5)	203 (50.9)	0.447
MASLD, *n*%	165 (8.9)	141 (13.4)	<0.001	75 (11.5)	66 (16.5)	<0.001

Values are mean ± SD or frequency (%). *P**subclinical hypothyroidism vs. low-normal thyroid function. Thyroid function: strict-normal, TSH 0.4–2.5 mIU/L; low thyroid function, TSH ≥2.5 mIU/L; low-normal, TSH 2.5–4.5 mIU/L; subclinical hypothyroidism, TSH ≥4.5 mIU/L.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HDL, high-density cholesterol; LDL, low-density cholesterol; T2DM Type 2 diabetes mellitus.

Table 3 Univariate and multivariate hazard ratio of thyroid dysfunction for the presence of MASLD

	Univariate		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Thyroid function						
Strict-normal	1		1		1	
Low-normal	1.29 (0.98–1.69)	0.069	1.34 (1.02–1.76)	0.038	1.30 (0.99–1.72)	0.060
Subclinical hypothyroidism	1.95 (1.47–2.60)	<0.001	1.86 (1.39–2.50)	<0.001	1.73 (1.29–2.33)	<0.001
Thyroid function						
Strict-normal	1		1		1	
Low thyroid function	1.53 (1.22–1.92)	<0.001	1.54 (1.22–1.93)	<0.001	1.47 (1.16–1.85)	0.001

Multivariate model 1 is adjusted for age and sex. Multivariate model 2 is adjusted for age, sex, hypertension, T2DM, total cholesterol, and triglycerides. Thyroid function: strict-normal, TSH 0.4–2.5 mIU/L; low thyroid function, TSH ≥2.5 mIU/L; low-normal, TSH 2.5–4.5 mIU/L; subclinical hypothyroidism, TSH ≥4.5 mIU/L.

was an independent risk factor of MASLD. However, our study did not detect any significant association between low-normal thyroid function and MASLD risk.

It is well known that thyroid hormones have direct effects on hepatic fatty acid and cholesterol synthesis and metabolism.[13] Hypothyroidism leads to elevated serum triglyceride and cholesterol levels. Given the potentially benefits of thyroid hormones on lipid metabolism, abnormal thyroid function may lead to metabolic disorders of the liver such as MASLD. Although many studies have been undertaken to investigate the association between hypothyroidism and fatty liver in the past, the relationship of NAFLD with thyroid function remains controversial and limited to NAFLD.[14] The studies investigating the association between low thyroid function and MASLD under new concepts and new diagnostic criteria have been insufficient. Some studies shown that subclinical hypothyroidism, even in the range of upper normal TSH levels (low-normal thyroid function), was found to be related to NAFLD in a dose-dependent manner,[15] but there were also studies pointing out that there was no correlation between NAFLD and low thyroid function.[16,17] In our study, low-normal thyroid function did not associate with MASLD, while low thyroid function is the independent risk factor of MASLD. The reason for the discrepancy between our findings and previous studies may be due to the difference between the definitions of MASLD and NAFLD. MASLD was proposed as a new definition to replace NAFLD recently. Although the variation in the definition was subtle, some studies have shown differences in risk factors and epidemiological characteristics between

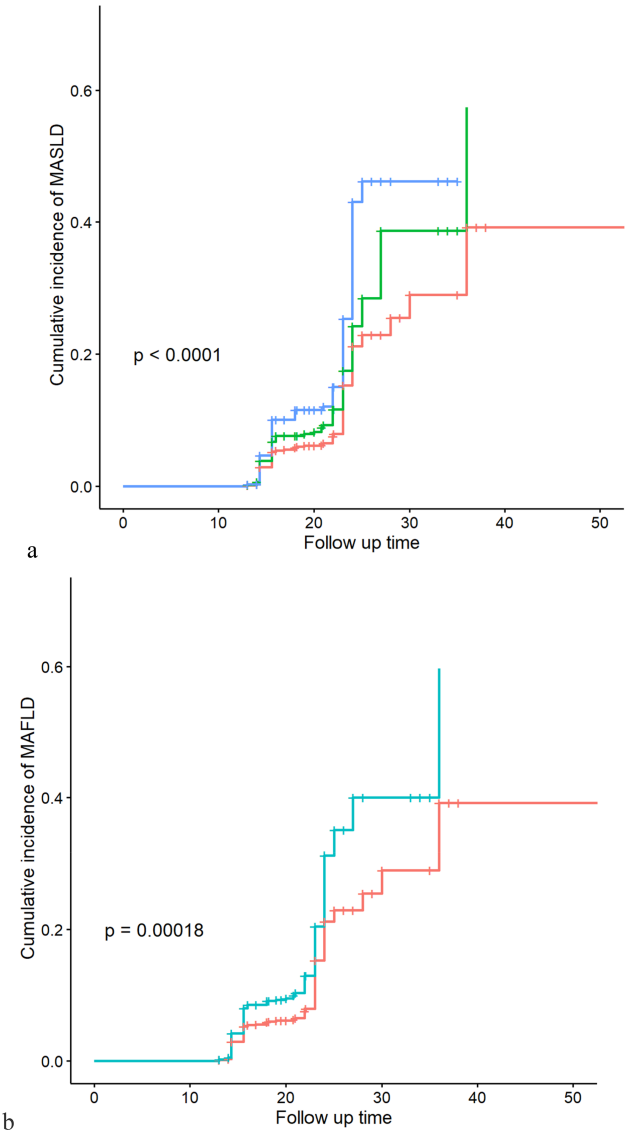

Figure 2 Kaplan–Meier curves for cumulative incidence of MASLD. (a) Cumulative MASLD incidence by —|—, strict-normal thyroid function; —|—, low-normal thyroid function; —|—, subclinical hypothyroidism. (b) Cumulative MASLD incidence by —|—, strict-normal thyroid function; —|—, low thyroid function.

MASLD and NAFLD.[8] It is worthy to note that although MASLD is associated with hypothyroidism, whether thyroid function can infer the severity of MASLD requires further study.[15]

MASLD is recognized as a multisystem disease that presents a wide spectrum of extrahepatic manifestations.[8] In addition to liver-related pathologies, it can increase the risk of metabolic syndrome, cardiovascular disease, and chronic kidney disease.[18–20] Although MASLD poses a serious global health burden, there are still no approved pharmacological therapies to prevent or treat this condition.[21] Therefore, discovering more risk factors associated with MASLD can help us prevent the development of MASLD at the source. The identification and better understanding of this association between thyroid function and MASLD from our study could help us find out a novel modality for the diagnosis, prognosis, and management of MASLD. This study had several limitations. The data we used were from one hospital in Shanghai, China; thus, extrapolation of our study is poor. Our data lacked waist circumference and alcohol consumption status, so potential cases of MASLD and MetALD cannot be identified. Despite these potential limitations, this study has several advantages. Compared with other cross-sectional studies, this study used a cohort study with a greater ability to verify causality, which can more strongly reflect the true association between hypothyroidism and MASLD. The diagnosis of MASLD in this study and the testing of other indicators were performed by specialized physicians, which strengthened our study.

In conclusion, MASLD is associated with low thyroid function, and the relationship between MASLD and low thyroid function is independent.

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Ethics statement

The study protocol was approved by the Human Research Ethical Committee of Shanghai University of Medicine & Health Sciences.

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